REMARKS

Status of the Claims and Specification Amendments

Claims 63-65 have been amended. Claim 66 is deleted. Therefore, after entry of this amendment, claims 63-65 will be pending.

The format and grammar of claim 63 has been modified to clarify that the term "consisting essentially of" modifies the term "oligopeptide," and that the term "consists of" modifies the term "N-terminal β-lactamase fragment." In addition, the K55E and P62S mutations have been removed, and the M182T mutation has been incorporated directly into the recited sequence.

Claims 63-65 have been amended to recite "polypeptide." Support for the term "polypeptide" may be found throughout the specification as filed, including for example, at page 5, lines 26-37, stating: "Compositions and methods are provided for identifying interactions between polypeptides using an interaction-dependent protein association system."

The specification has been amended to cancel the previously submitted sequence listing and to insert therefore a substitute sequence listing. The substitute sequence listing is necessitated by the addition of a new sequence no. 27 in claim 63. Applicants request entry of this amendment in adherence with 37 C.F.R. §§1.821 to 1.825. This amendment is accompanied by a compact disk containing the sequences, SEQ ID NOS:1-27, in computer readable form, and a paper copy of the sequence information which has been printed from the compact disk. The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy.

Therefore, no new matter is added with this amendment.

35 U.S.C. § 112, Second Paragraph: Indefinite

The Examiner has rejected the claims as indefinite for recitation of the phrase "consisting essentially of." The Examiner asserts that it is not clear whether the term "consisting essentially of" allows conservative substitutions within the sequence of the N-terminal β-lactamase fragment.

Applicants have amended the format and grammar of claim 63 to clarify that an N-terminal β-lactamase fragment having conservative substitutions of the recited β-lactamase sequence is not encompassed by the claim.

In amended claim 63, a hierarchical structure is set forth to clearly separate the polypeptide term from the N-terminal β-lactamase fragment term. The phrase "consists essentially of" clearly modifies the polypeptide term only. Thus, the phrase "consists essentially of" limits the scope of the polypeptide to the specified components "and those that do not materially affect the basic and novel characteristic(s)" of the claimed polypeptide. See *In re Herz*, 537 F.2d 549 (CCPA 1976). The specified components are: (1) an interactor, (2) a linker, and (3) an N-terminal β-lactamase fragment. Accordingly, the polypeptide is limited to an interactor, a linker, an N-terminal β-lactamase fragment, and other components that do not affect the basic and novel characteristics of the polypeptide.

The nature of the claimed N-terminal β-lactamase fragment is separately addressed in the subsequent portion of the hierarchical structure. In item (a), the claim specifies that the N-terminal β-lactamase fragment component of the polypeptide contains only the specified amino acids of the recited β-lactamase sequence. The term "consists of" modifies only the term "N-terminal β-lactamase fragment," thereby limiting the N-terminal β-lactamase fragment component to the specified amino acids of the recited β-lactamase sequence. Applicants submit that one skilled in the art would understand that the term "consists of" indicates that an polypeptide having an N-terminal β-lactamase fragment with conservative substitutions in the recited β-lactamase sequence would not be covered.

In view of the amendments to claim 63, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

35 U.S.C. § 112, First Paragraph: Enablement

The Examiner has rejected claims 63-69 as allegedly nonenabled. The Examiner asserts:

1. The term "consisting essentially of" is indefinite;

2. Galarneau et al. only teach the M182T mutant;
3. The fact that Galarneau et al. was published in the prestigious journal *Nature* is evidence that the application was non-enabled when filed;
4. The current claim language requires the addition of a complimentary C-terminal β-fragment; and
5. A statement in the specification regarding the utility of the present invention in prokaryotic cells is false and leads away from the present invention.

As a preliminary matter, Applicants note that claim 63 has been amended to clarify that an N-terminal β-lactamase fragment having conservative substitutions in the recited β-lactamase sequence are not encompassed by the claim. Therefore, Applicants respectfully submit that the first point is now moot.

In response to the second point, Applicants note that claim 63 has been amended to include only the M182T mutant. Therefore, Applicants submit that the second point is now moot.

With regard to the third point, Applicants respectfully note that the present U.S. application has not been published. Therefore, the present U.S. application could not have been reviewed by *Nature* referees prior to the acceptance of the Galarneau et al. paper. Applicants note that the corresponding PCT application published on November 30, 2000. However, the PCT application was not referenced in the Galarneau et al. paper. Therefore, there is no evidence that the PCT application was reviewed by referees for the journal *Nature* prior to the acceptance of the Galarneau et al. paper. Thus, Applicants respectfully submit that the fact that Galarneau et al. was published in the prestigious journal *Nature* is irrelevant to the present enablement analysis.

In reference to the fourth point, Applicants note that claim 63 currently recites "a C-terminal β-lactamase enzyme fragment consisting of amino acids 288 to 208 up to amino acid 189 of said β-lactamase sequence." Therefore, Applicants submit that the current claim language includes a C-terminal β-fragment. If the Examiner still believes that the current claim language

"requires addition of the essential complimentary C-terminal β-fragment," Applicants request the Examiner explain why the current language is inadequate.

Finally, the Examiner raises doubt as to the objective truth of Applicants' statement that "[a]ppropriate host cells for application of the subject invention include both eukaryotic cells, such as mammalian, yeast and plant cells, and prokaryotic cells, such as bacterial cells." See page 12, lines 6-9. The Examiner points to Example 7, which shows that in one embodiment of the invention, there is no interaction dependence of the complementation system in a prokaryotic cell. The Examiner asserts that the statement at page 12 and Example 7 are contradictory and would impede rather than enable one skilled in the art to practice the claimed invention. Applicants respectfully disagree.

At page 6, lines 5-9, the specification summarizes the subject invention as a complementation system with fragment pairs that include a cysteine residue ***or*** a "1-3 codon" change (such as M182T) ***or*** a randomly encoded peptide of from 3-12 amino acids (such as a tripeptide). Example 7 merely demonstrates that in one particular cell type (prokaryotic cells), one particular embodiment of the subject invention (an α197 fragment having a "1-3 codon" change) fails to show interaction dependence. However, Example 7 also demonstrates successful interaction dependence in another embodiment of the invention, where the N-terminal β-lactamase fragment is an α197 fragment having a randomized tripeptide.

Because Example 7 demonstrates successful interaction dependence with one embodiment of the subject invention, Applicants respectfully submit that the results do not contradict the statement that "[a]ppropriate host cells for application of the subject invention include both eukaryotic cells, such as mammalian, yeast and plant cells, and prokaryotic cells, such as bacterial cells."

Applicants further submit that one skilled in the art would understand the complexities of the results shown in Example 7. As stated by the Examiner, the level of one of ordinary skill in the art would be high, most likely at the Ph.D. level. Applicants respectfully submit that a Ph.D. scientist is more than capable of reading Example 7 and understanding the results in the context of Applicants' statement at page 12, lines 6-9, where prokaryotic cells are

included in a list of possible host cells for the subject invention. Because a Ph.D. scientist would understand that prokaryotic systems differ from eukaryotic systems, results obtained in prokaryotic cells would not lead a Ph.D. level scientist away from the use of the claimed invention in eukaryotic cells. Rather, after reading Example 7, one skilled in the art would merely be led away from practicing a complementation system in bacteria with an α197 fragment in the absence of a randomized tripeptide.

Even assuming *arguendo* that the Examiner has properly raised a doubt as to the objective truth of Applicants' disclosure, Applicants submit that they have overcome the rejection by providing suitable proof of enablement by providing the Galarneau *et al.* reference. The Examiner is respectfully reminded that:

> As a matter of Patent Office practice ... a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 ***unless there is reason to doubt the objective truth of the statements contained therein*** which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection ***can be overcome by suitable proofs*** indicating that the teaching contained in the specification is truly enabling....
> Most often, additional factors, such as the ***teachings in pertinent references[4], will be available to substantiate any doubts*** that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof.
>
> [4] ***Not necessarily prior art references***, it should be noted, since the question would be regarding the *accuracy* of a statement in the specification, not whether that statement had been made before (emboldened emphasis added). See *In re Marzocchi and Horton* 169 USPQ 367 (CCPA) (1971).

In light of the amendments to the claims, Applicants submit that the Galarneau et al. reference fully validates Applicants' teachings in the specification. Absent a reason as to why Galarneau et al. would not constitute a suitable proof, Applicants submit that the Examiner's

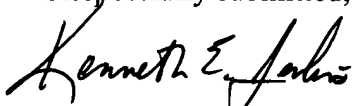
rejection, even if proper, has been overcome. Therefore, Applicants respectfully request that the rejection based on 35 U.S.C. § 112, first paragraph be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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